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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/492,029	01/26/2000	Charles S. Zuker	2307E-92710US	9362

7590 04/09/2003

TOWNSEND TOWNSEND & CREW
TWO EMBARCADERO CENTER 8th FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	19

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/492,029	Applicant(s) ZUKER ET AL.	
	Examiner Manjunath N. Rao, Ph.D.	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24,28 and 29* is/are rejected.

7)☒ Claim(s) *25-27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-29 are now at issue and are present for examination.

Applicants' amendments and arguments filed on 4-1-02 and 4-4-02, paper Nos. 15 and 17, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claims 25-27 are objected to because of the following informalities: Claims 25-27 recite the abbreviations GPCR-B3, GPCR-B4 and HEK-93, respectively, without providing proper expansions of the abbreviations. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-24, 28-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Margolskee et al. (WO 93/21337, 10-28-1993), Bruch et al. (JBC, 1987, Vol. 262(5):2401-2404), Levine et al. (Proc. Natl. Acad. Sci. USA, 1990, Vol. 87:2329-2333) or Ray et al. (Gene, 1994, Vol. 149:337-340) and Negulescu et al. (WO 97/48820, 12-24-1997). Claims 1-24, 28-29 in this instant application are basically drawn to a method of identifying a compound that modulates

sensory signaling in taste cells comprising contacting a compound with a taste cell specific G-protein β polypeptide which has greater than 70% amino acid sequence identity to or has the amino acid sequence with SEQ ID NO:3 or 5 and determining the functional effect of the compound upon the polypeptide wherein the functional effect is determined by either measuring change in intracellular concentration of specific cyclic nucleotides or Ca2+ and wherein the polypeptide is expressed in a cell or a cell membrane. The claims are also directed to methods wherein the functional effect is determined by changes in electrical activity measured by voltage clamp assay or a patch clamp assay etc. and wherein the functional effect is determined by measuring changes in transcription levels of taste cell specific genes and wherein the polypeptides are recombinant or covalently linked to a solid phase support and wherein the polypeptide is from mouse, rat or human or has an amino acid sequence of SEQ ID NO:3 or 5. Claims are also drawn to a method of identifying a compound that modulates the taste signaling comprising expressing the taste cell specific G-protein ß polypeptide, expressing a promiscuous G-protein α polypeptide as well, wherein the promiscuous G-protein α polypeptide is Gα14 or G α15.

Margolskee et al. teach in detail regarding the mechanisms involved vertebrate taste transduction. The reference also teaches that guanine nucleotide binding proteins (G proteins) are heterotrimeric proteins (each having an α , β, and γ sub unit) which mediate signal transduction in olfactory, visual, hormonal and neurotransmitter systems. The reference teaches G proteins are specifically involved in taste transduction. The reference teaches that G proteins couple cell surface receptors to cellular effector enzymes (i.e., phosphodiesterases and adenylate cyclases) and thereby transduce extracellular signals into intracellular second messenger (e.g.,

cAMP, cGMP, IP3 etc.). The reference also teaches that while α subunit of G protein confers most of the specificity of interaction between its receptor and its effectors in signal transduction process, β and γ subunits appears to be shared among different G proteins. Thus it appears that it was well known in the art that cyclic nucleotides such as cAMP, cGMP along with G proteins are very much involved in the transduction of taste. The above reference also reveals the involvement of Ca2+ in transduction of taste and involvement of G-proteins. The reference also suggests that compounds with taste lead to taste cell depolarization *via* a G protein mediated rise in cAMP. For example, bitter compounds lead to Ca2+ release from internal stores which is a result of G- protein mediated generation of IP3.

The reference also teaches that over the past decade, efforts have been directed to the development of various agents that interact with taste receptors or mimic or block natural taste stimulants. However, some such taste mimetics have been known not to be suitable for humans either because of high calories they carry or because they are potent carcinogens. Therefore development of new agents that mimic taste or block taste have been limited due to the lack of knowledge of the taste cell proteins responsible for transducing taste modalities and thus there continues to exist a need in the art for new products and methods that are involved in or affect taste transduction. Furthermore, the above reference provides the DNA encoding α subunit called as gustducin of the G-protein involved in taste transduction. The reference also provides methods to identify taste modifying agents which involves identifying agents capable of modulating (mimicking or inhibiting) the interaction of gustducin. Out of the several methods Margolskee et al. propose, one of the method taught is the method of identifying a compound which modulates the activity of the α subunit of the sensory cell associated G-protein by

contacting the compound with the α polypeptide only or with α , β and γ polypeptides associated in biologically active form and a radioactively labeled GTP followed by the determination of the rate of conversion of GTP to GDP, which is very similar to the method proposed in the instant for the β polypeptide. However, the reference does not teach an assay exclusively for identifying a compound that modulates taste signaling in taste cells comprising contacting a compound with a taste cell specific G-protein ß polypeptide or a polypeptide which has an amino acid sequence with SEQ ID NO:3 or 5 or any polypeptide which is 70% identical to SEQ ID NO:3 or 5. The reference is also silent on certain other types of assays such as the use of patch clamp technique or radio labeled ion flux assay etc. even though such techniques have become routine in the art and are well known for studying signal transduction in various types of cells. Bruch et al. for the first time teach the involvement of the common G-protein beta subunit in the taste plasma membranes that stimulates adenylate cyclase and therefore its involvement in signal transduction in taste cells. The reference teaches that G-protein ß subunit was identified by immunoblotting and stimulated adenylate cyclase and co-migrated with the α subunit of the G-protein. While the reference does not teach the amino acid sequence of the ß subunit, Examiner takes the position that such amino acid sequences are inherent to the polypeptide and therefore the reference ß subunit has an amino acid sequence that is identical to that of either SEQ ID NO:3 or 5 or that its amino acid sequence is greater than 70% identical to that of SEQ ID NO:3 or 5. While the reference does not explicitly teach an assay for identification of compounds that modulate sensory signaling in cells, it does teach an assay for the ß subunit of the G-protein and its involvement in taste signal transduction. (Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art,

the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594).

Ray et al. teach the cloning of the β polypeptide of sensory cell G-protein which has 100% identity to SEQ ID NO:3. The reference provides cDNA techniques and methods to make recombinant β polypeptide.

Levine et al. teach the cloning of the β polypeptide of sensory cell G-protein which has 97% identity to SEQ ID NO:5. The reference provides cDNA techniques and methods to make recombinant β polypeptide.

Negulescu et al. teach the use of promiscuous G-proteins and their use in identifying G-protein receptors and ligands and compounds that modulate signal transduction. The reference specifically teaches compositions and methods that employ promiscuous G-proteins such as G α 15, detection of activation of promiscuous G-proteins n a variety of assays, including assays in which activation is indicated by a change in fluorescence emission.

Thus it appears that the involvement of the ß subunit of G-proteins in taste signal transduction was well known in the art that there was a concerted effort in the art for identifying compounds which modulate the activity of such G-protein sub units. It also appears that a method for assaying compounds which modulate sensory cell G-protein was also well known in the art. Based on the above knowledge and with the knowledge that the sensory cell G-protein comprises of α, β, and γ polypeptides, and the specific involvement of ß subunit in taste signal transduction as taught by Bruch et al. it would have been obvious to one of ordinary skill in the

art to identify agents that specifically modulate the activity of G-proteins in general and β subunit in particular. As Margolskee et al. teach, one would be motivated to do this in order to identify agents which mimic or block taste and thus such compounds have commercial importance in food and pharmaceutical industry and also due to the fact that some of the known agents are unsuitable for human consumption. One would have a reasonable expectation of success since Bruch et al. clearly show the involvement of ß subunit in taste signal transduction, Margolskee et al. and Negulescu et al. lay the foundation for such methods and also isolate compounds which modulate one of the other factors of sensory cell G-protein, the α polypeptide. Levine et al. and Ray et al. further provide cDNA clones for the β polypeptide of sensory cell G-protein to be used by one skilled in the art contemplating on recombinant methods of expression of such polypeptides.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office action applicants have mainly argued that Margolskee et al. while, disclosing Gustducin, a G-protein α subunit specifically expressed in taste cells, does not disclose the taste cell specific G-protein ß subunits of the present invention and that while Ray et al. and Levine et al. disclose the sequence identity of the claimed ß subunits, those polypeptides were cloned from heart cDNA library and have shown its expression in heart and brain but not in taste cells of the tongue. Applicants continue to traverse the rejection as if the rejection was written against the amended claims wherein applicants have now limited their claims to "taste cells". Examiner respectfully disagrees with such an argument. While the reference of Margolskee et al. is directed towards identification of compounds that modulate the

activity of an α subunit of a G-protein in taste signal transduction, the publication does refer to other subunits such as the ß and the γ. Examiner maintains his argument that Margolskee et al. by itself does contribute towards the obviousness of the claims. However, in order to support his rejection and counter the arguments by applicants that Margolskee et al. does not teach involvement of ß subunit in taste signal transduction, Examiner has now provided the reference of Bruch et al. which links the involvement of ß subunit with taste modalities. Applicants' argument that the present invention demonstrates for the first time a G-protein ß subunit preferentially expressed in taste cells of the tongue is misplaced since Bruch et al. were the first to report involvement of ß subunit in taste signal transduction. Examiner respectfully disagrees with the applicants that he concluded the obviousness of the above invention without identifying the principles that would motivate one of skill in the art to combine the cited references and used hindsight reconstruction. This is because, Margolskee et al. teach the importance of identification of compounds that modulate the taste signal transduction in general and while specifically directing their invention to identify compounds that modulate gustducin, the reference does provide a suggestion that compounds that modulate either α, ß or γ have commercial value in food and pharmaceutical industry. Therefore, there was motivation and also a reasonable expectation of success in the art for identifying compounds that modulate taste signal transduction in general and applicant's argument that one of skill in the art would have arrived at such a conclusion only after reading the applicant's specification is highly misplaced. While Examiner agrees that Ray et al. and Levine et al. isolated the G-protein subunit from a different tissue, Examiner has used the references only to show that their amino acid sequences were available for those skilled in the art. Both the above references are used to further support

the rejection. Therefore, even without the references of Ray et al. and Levine et al. above claims would have been rendered obvious by Bruch et al. and Margolskee et al. as they teach the main substance of the above invention. Therefore for all the above reasons the rejection is maintained.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection using new references presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Manjunath N. Rao Ph.D.
4/1/03

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1300~~ 1600